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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/GB93/02592</p> <p>(22) International Filing Date: 17 December 1993 (17.12.93)</p> <p>(30) Priority Data: 9300051.1 4 January 1993 (04.01.93) GB</p> <p>(71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): TEALL, Martin, Richard [GB/GB]; Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). WILLIAMS, Brian, John [GB/GB]; Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p> <p>(74) Agent: COLE, William, Gwyn; Merck & Co., Inc., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p>		<p>(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published With international search report.</p>
<p>(54) Title: 3,3 DIPHENYL PROP-2-YL AMINO ACID DERIVATIVES AND THEIR USE AS TACHYKININ ANTAGONISTS</p>		
<p>(57) Abstract</p> <p>Compounds of formula (I), or a salt or prodrug thereof, wherein R¹ represents H, C₁₋₄alkyl or CH₂COOH; R² represents H or C₁₋₄alkyl, with the proviso that R¹ and R₂ are not both H; R³ and R⁴ each independently represent H, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, halo or trifluoromethyl; A¹, A², A³ and A⁴ each independently represent H, C₁₋₆alkyl, C₁₋₆alkenyl, C₁₋₆alkoxy, halo or trifluoromethyl; and A⁵ and A⁶ each independently represent H or C₁₋₄alkyl are tachykinin antagonists useful as medicaments.</p> <div style="text-align: center;"> <p>(1)</p> </div>		

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3,3 Diphenyl prop-2-yl amino acid derivatives and their use as tachykinin antagonists

5 This invention relates to a class of aromatic compounds which are useful as tachykinin antagonists. More particularly, the compounds of the invention contain a diphenyl moiety and a substituted amine moiety.

The tachykinins are a group of naturally occurring peptides found widely distributed throughout
10 mammalian tissues, both within the central nervous system and in peripheral nervous and circulatory systems.

The structures of three known mammalian tachykinins are as follows:

Substance P:

15 Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH₂

Neurokinin B:

Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH₂

20 For example, substance P is believed inter alia to be involved in the neurotransmission of pain sensations [Otsuka et al, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba
25 Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" TIPS (Dec. 1987) 8 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg et al, J. Med Chem, (1982) 25 1009) and in arthritis
30 [Levine et al in Science (1984) 226 547-549]. These peptides have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh et al in Neuroscience (1988) 25 (3) 817-37 and D. Regoli in "Trends in Cluster

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Headache" Ed. Sicuteri et al Elsevier Scientific Publishers, Amsterdam (1987) page 85)]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd et al "A Neurogenic Mechanism for Symmetrical Arthritis" in The Lancet, 11 November 1989 and Grönblad et al "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in J. Rheumatol. (1988) 15(12) 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis, and fibrositis [O'Byrne et al in Arthritis and Rheumatism (1990) 33 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66 1361-7], immunoregulation [Lotz et al Science (1988) 241 1218-21 and Kimball et al, J. Immunol. (1988) 141 (10) 3564-9] vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh et al, PNAS (1988) 85 3235-9] and, possibly by arresting or slowing β -amyloid-mediated neurodegenerative changes [Yankner et al Science (1990) 250, 279-82] in senile dementia of the Alzheimer type, Alzheimer's disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod et. al., poster to be presented at C.I.N.P. XVIIIth Congress, 28th June-2nd July, 1992], and in disorders of bladder function such as bladder detrusor hyper-reflexia (Lancet, 16th May, 1992, 1239).

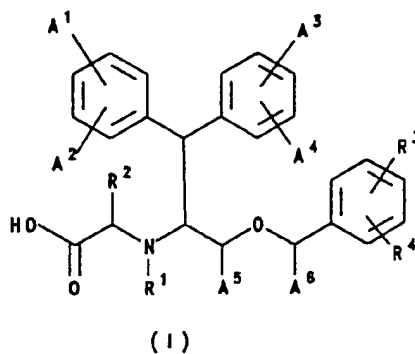
It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as

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poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophillic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosis (European patent application no. 0 436 334), opthalmic disease such as conjunctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989).

We have now found a class of non-peptides which are potent antagonists of tachykinin.

The present invention provides a compound of formula (I), or a salt or prodrug thereof:



wherein

R¹ represents H, C₁₋₄alkyl or CH₂COOH;

R² represents H or C₁₋₄alkyl, with the proviso

that R¹ and R² are not both H;

R³ and R⁴ each independently represent H, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, halo or trifluoromethyl;

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A¹, A², A³ and A⁴ each independently represent H, C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkoxy, halo or trifluoromethyl and A⁵ and A⁶ each independently represent H or C₁₋₄ alkyl.

5 The alkyl groups referred to with respect to any of the formulae herein may represent straight, branched or cyclic groups. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, 10 cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl.

 The term "halo" as used herein includes fluoro, chloro, bromo and iodo, preferably chloro.

 Preferably R¹ represents H, methyl, ethyl or 15 CH₂COOH, more preferably methyl.

 Preferably R² represents H or methyl, more preferably H.

 Preferably R³ and R⁴ are selected from methyl, ethyl, t-butyl, chloro, bromo and trifluoromethyl, more 20 preferably methyl and trifluoromethyl. Preferred are compounds wherein R³ and R⁴ are located at the 3- and 5-positions of the phenyl ring.

 Favourably A¹, A², A³ and A⁴ each independently represent H, F, Cl, Br, CF₃, CH₃ or OCH₃.

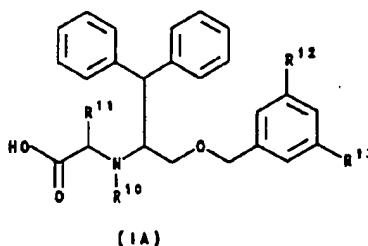
25 A represents H or F, A² represents H, A³ represents H or F and A⁴ represents H.

 Preferably A¹, A², A³ and A⁴ each represent H.

 A⁵ and A⁶ each independently represent H or CH₃. Favourably A⁵ and A⁶ both represent H.

30 A preferred subgroup of compounds according to the invention is represented by compounds of formula (IA) and salts and prodrugs thereof:

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wherein

R^{10} represents H, methyl or CH_2COOH ;

10 R^{11} represents H, methyl or ethyl, with the proviso that when R^{10} is H, R^{11} is not H; and

R^{12} and R^{13} each independently represent

C_{1-6} alkyl, such as t-butyl, methyl or ethyl, C_{2-6} alkenyl, such as vinyl, C_{1-6} alkoxy, such as methoxy, halo, such as
15 chloro or bromo, or trifluoromethyl.

Specific compounds according to the present invention include:

(S)-N-(1-((3,5-bis(trifluoromethyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

20 (S)-N-(1-((3-t-butyl-5-chloro)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

(S)-N-(1-((3,5-dimethyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

25 (S)-N-(1-((3-chloro-5-methyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

(S)-N-(1-((3-bromo-5-methyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

(S)-N-(1-((3,5-dichlorophenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

30 (S)-N-(1-((3-methyl-5-vinyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

(S)-N-(1-((3-ethyl-5-methyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

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(S)-N-(1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenylprop-2-yl)alanine;

(S)-2-(N,N-bis(carboxymethyl)amino)-1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-

5 diphenylpropane;

(S)-N-(1-((3-methoxy-5-methyl)phenyl)methyloxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

(S)-N-(1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenylprop-2-yl)-N-ethylglycine;

10 and salts and prodrugs thereof.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the

15 invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid

addition salts which may, for example, be formed by mixing a solution of the compound according to the

20 invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups

25 may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable

30 salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

Preferred salts of the compounds of formula (I) include the tosylate, oxalate, bisoxalate, iodide,

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hydrobromide and hydrochloride salts. Particularly preferred are the hydrochloride and hydrobromide salts.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In
5 general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are
10 described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

15 The compounds according to the invention have at least one asymmetric centre, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.
20 Preferably the stereochemistry at the carbon to which the benzhydryl moiety is attached is S.

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I), or salts or prodrugs thereof,
25 in association with a pharmaceutically acceptable carrier.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral
30 solutions or suspensions, or suppositories, for oral, parenteral or rectal administration. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch,

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lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils

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such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums
5 such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

The present invention further provides a process for the preparation of a pharmaceutical composition
10 comprising a compound of formula (I), or a salt or prodrug thereof, which process comprises bringing a compound of formula (I), or a salt or prodrug thereof into association with a pharmaceutically acceptable carrier or excipient.

15 The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such
20 as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such
25 as peripheral neuropathy, for example diabetic and chemotherapy-induced neuropathy, and postherpetic and other neuralgias; respiratory diseases such as chronic obstructive airways disease, bronchopneumonia, bronchospasm and asthma; cystic fibrosis; inflammatory
30 diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like;

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cutaneous diseases such as contact dermatitis, atropic
dermatitis, urticaria, and other eczematoid dermatitis;
addiction disorders such as alcoholism; stress related
somatic disorders; reflex sympathetic dystrophy such as
5 shoulder/hand syndrome; dysthymic disorders; adverse
immunological reactions such as rejection of transplanted
tissues and disorders related to immune enhancement or
suppression such as systemic lupus erythematosus;
gastrointestinal (GI) disorders and diseases of the GI
10 tract such as disorders associated with the neuronal
control of viscera such as ulcerative colitis, Crohn's
disease and incontinence; disorders of bladder function
such as bladder detrusor hyper-reflexia; fibrosing and
collagen diseases such as scleroderma and eosinophilic
15 fascioliasis; disorders of blood flow caused by
vasodilation and vasospastic diseases such as angina,
migraine and Reynaud's disease; and pain or nociception,
for example, that attributable to or associated with any
of the foregoing conditions, especially the transmission
20 of pain in migraine. For example, the compounds of
formula (I) may suitably be used in the treatment of
disorders of the central nervous system such as anxiety,
psychosis and schizophrenia; neurodegenerative disorders
such as senile dementia of the Alzheimer type,
25 Alzheimer's disease and Down's syndrome; respiratory
diseases such as bronchospasm and asthma; inflammatory
diseases such as inflammatory bowel disease,
osteoarthritis and rheumatoid arthritis; adverse
immunological reactions such as rejection of transplanted
30 tissues; gastrointestinal (GI) disorders and diseases of
the GI tract such as disorders associated with the
neuronal control of viscera such as ulcerative colitis,
Crohn's disease and incontinence; disorders of blood flow
caused by vasodilation; and pain or nociception, for

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example, that attributable to or associated with any of the foregoing conditions or the transmission of pain in migraine.

5 The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis
10 and especially migraine.

 The present invention thus provides a compound of formula (I), or a salt or prodrug thereof, for use in therapy.

 The present invention further provides a
15 compound of formula (I), or a salt or prodrug thereof, for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P. The present invention also provides a method for the the
20 treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I), or a salt or prodrug
25 thereof.

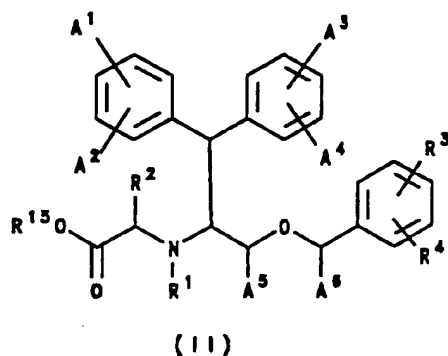
 In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10
30 mg/kg per day. For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The

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compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

The compounds according to the invention may be prepared by saponification of a compound of formula (II)

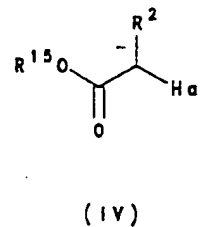
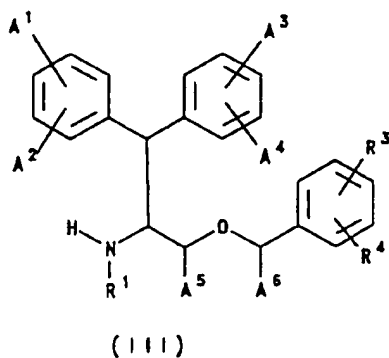
5



wherein R^1 , R^2 , R^3 , R^4 , A^1 , A^2 , A^3 , A^4 , A^5 and A^6 are as defined for formula (I) above and R^{15} represents C_1 -
 15 alkyl, using conventional methods.

Conveniently the saponification is carried out using an alkali metal hydroxide, such as, for example, sodium hydroxide, in water or an aqueous solvent,
 20 suitable at room temperature.

Compounds of formula (II) may be prepared by reaction of compounds of formula (III) with compounds of formula (IV):

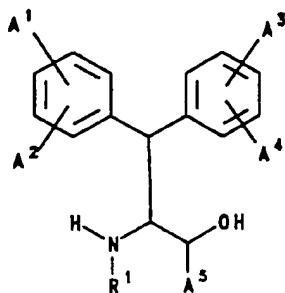


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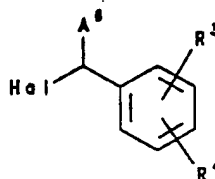
wherein R^1 , R^2 , R^3 , R^4 , A^1 , R^{15} , A^2 , A^3 , A^4 , A^5 , and A^6 are as previously defined and Hal represents halo such as chloro or, preferably bromo, in the presence of a base.

Suitable bases of use in the reaction include
 5 alkali metal hydrides, such as, for example, sodium hydride, and alkali metal carbonates, such as for example, potassium carbonate. The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, tetrahydrofuran.

10 Compounds of formula (III) may be prepared by reaction of intermediates of formula (V) with intermediates of formula (VI):



(V)



(VI)

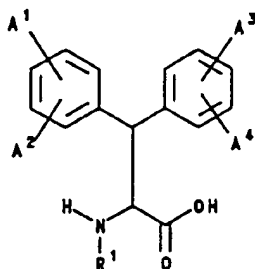
wherein R^1 , R^3 , R^4 , A^1 , R^{15} , A^2 , A^3 , A^4 , A^5 , and A^6 and Hal are as previously defined, in the presence of a base.

Suitable bases of use in the reaction include
 25 alkali or alkaline earth metal hydrides, for example, sodium hydride.

The reaction is conveniently carried out in a suitable organic solvent, such as an ether, for example, tetrahydrofuran, suitably at ambient temperature.

30 Compounds of formula (V) may be prepared from the corresponding compounds of formula (VII)

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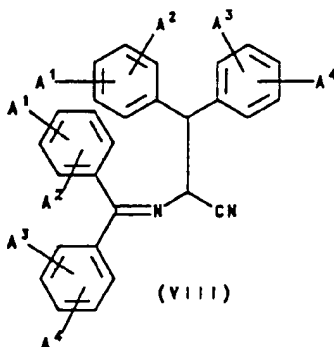
(VII)

10 wherein R¹, A¹, A², A³, and A⁴ is as previously defined
by using conventional methods.

Suitable reducing agents include metal
hydrides, such as lithium aluminium hydride. The
reaction is conveniently effected in a suitable organic
15 solvent, such as an ether, for example, tetrahydrofuran,
suitably at elevated temperature, such as the reflux
temperature of the solvent.

Intermediates of formula (VII) wherein R¹ is H
may be prepared from the intermediate of formula (VIII)

20



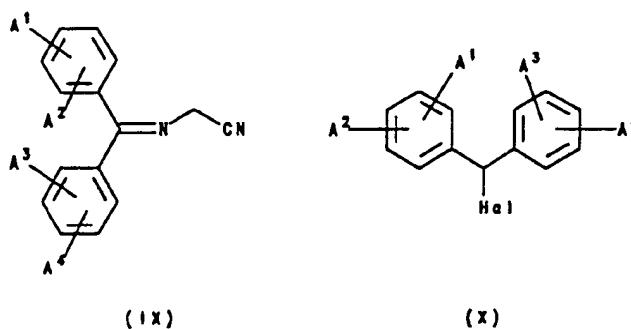
(VIII)

by hydrolysis.

30 The reaction is conveniently effected by
heating a solution of the compound of formula (VIII) in
concentrated hydrochloric acid at reflux.

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The compound of formula (VIII) may be prepared by reaction of the compound of formula (IX) with a compound of formula (X):



wherein Hal is as previously defined, in the presence of a base.

15 Suitable bases of use in the reaction include metal hydroxides, for example, sodium hydroxide. The reaction is conveniently effected in a mixture of water and a suitable organic solvent, such as a hydrocarbon, for example, toluene, in the presence of a phase transfer
20 catalyst, such as benzyltrimethyl ammonium chloride.

The compound of formula (IX) is commercially available.

Compounds of formula (X) may be prepared according to the procedure described by E. J. Corey,
25 Tetrahedron Lett., 1972, 4339, or by other conventional procedures which will be readily apparent to those skilled in the art.

It will be apparent to those skilled in the art that compounds of formula (I), (II), (III), (V) or (VII) wherein R¹ is other than H may be prepared from the
30 corresponding compounds wherein R¹ is H by reaction with an alkylating agent, for example, a halide of formula R¹-Hal, under conventional conditions.

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Compounds of formulae (IV) and (VI) are commercially available or may be prepared by conventional procedures well known to those skilled in the art.

Where the above-described process for the
5 preparation of the compounds according to the invention gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic
10 form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with
15 an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides,
20 for example, leucine methyl esters, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or
25 reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wutts, Protective Groups in
30 Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

EXAMPLE 1(S)-N-(1-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine

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a) To a solution of diphenylmethylenimineacetonitrile (44g, 0.20mol), benzyltrimethyl ammonium chloride (4.4g, 0.024mol) and sodium hydroxide (48.4g, 1.21mol) in toluene (40ml) and water (90ml) was added bromodiphenylmethane (149g, 0.60mol) at 0°C. After the solution had been stirred at room temperature for 5h a mixture of water (200ml), ethyl acetate (40ml) and hexane (160ml) was added. The solution was filtered and the residue washed with ethyl acetate/hexane and dried *in vacuo* to give 3,3-diphenyl-2-(diphenylmethylenimine)propionitrile 47.6g. ¹H NMR (360MHz, CDCl₃) δ 7.5-6.87 (20H, m, aryl), 4.8 (1H, d, J = 8.85Hz), 4.69 (1H, d, J = 9.2Hz). An analytical sample was recrystallised from ethyl acetate/hexane mp = 152-153°C.

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b) 3,3-Diphenyl-2-(diphenylmethylenimine)propionitrile (Example 1a, 46.7g, 0.12mol) was heated in a solution of 5.5M-hydrochloric acid (200ml) at reflux for 48h. The solid which crystallised from the cooled solution was removed by filtration, washed with diethyl ether and dried to give β,β-diphenylalanine hydrochloride 21g. ¹H NMR (250MHz, DMSO d₆) δ 8.6 (3H, vbs), 7.6-7.1 (10H, m), 4.8 (1H, d, J = 10.4Hz), 4.4 (1H, d, J = 10.4Hz).

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c) A solution of β,β-diphenylalanine hydrochloride (2.5g, 9.01mmol), di-t-butylidicarbonate (3.0g, 14.02mmol) and

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- triethylamine (2.6ml) in dichloromethane (50ml) was heated at reflux for 0.5h. To the solution was added N,N-dimethylethylenediamine (0.49ml) and the solution allowed to cool to room temperature. To the solution was added aqueous citric acid and the organic phase was washed with water, saturated brine and dried (MgSO_4). To the residue, obtained after removal of the solvent *in vacuo*, was added diethyl ether (30ml) and dicyclohexylamine (1.63g), to give after filtering and drying N-t-butoxycarbonyl- β,β -diphenylalanine dicyclohexylamine salt, 4.7g mp 154-154.5°C. ^1H NMR (250MHz, CDCl_3) δ 7.4-7.0 (10H, m), 5.0 (1H, d, $J = 9.5\text{Hz}$), 4.7 (1H, dd), 4.5 (1H, d, $J = 7.05\text{Hz}$), 2.8 (2H, m), 1.9-1.5 (10H, m), 1.4-1.0 (19H, m). m/z (Cl^-) 340 (M-H).
- d) 2-t-Butoxycarbonyl- β,β -diphenylalanine dicyclohexylamine salt (Example 1c, 75.4g, 0.144mol) was liberated from its dicyclohexylamine salt by extraction in ethyl acetate from an aqueous citric acid solution, followed by washing (water and saturated brine) and drying (MgSO_4). The solvent was removed *in vacuo* to give a crystalline mass of the free acid. This solid was dissolved in dimethylformamide (200ml) and to this solution, cooled to 0°C, was added 1-hydroxybenzotriazole (26.4g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (33.1g). After stirring the solution at 0°C for 30 minutes a solution of L-leucine methyl ester hydrochloride (31.4g) and triethylamine (24.0ml) in dimethylformamide (50ml) was added. The solution was stirred at room temperature for 16h and then ethyl acetate (500ml) and 10% aqueous citric acid (500ml) were added. The organic phase was washed successively with 10% citric acid, 10% aqueous sodium carbonate, water, saturated brine and dried (MgSO_4). The solvent was removed *in*

vacuo to give N-t-butyloxycarbonyl-diphenylalanyl-L-leucine methyl ester as a mixture of diastereomers (approximately 1:1). To the above solid was added anhydrous trifluoroacetic acid (100ml). After a total of 30 minutes the solvent was removed *in vacuo* and a solution of the residue in ethyl acetate was washed successively with 10% aqueous carbonate, saturated brine and dried (MgSO₄). The solvent was removed *in vacuo* and upon addition of ethyl acetate/hexane (1:1) a crystalline solid, 19.63g was formed. After removal by filtration, and recrystallisation from ethyl acetate/hexane (1:1) this gave a pure sample of D-β,β-diphenylalanyl-L-leucine methyl ester, 12.14g.

The combined mother liquors were evaporated to dryness and applied to a column containing silica gel. Elution with ethyl acetate/hexane (1:1) gave pure L-β,β-diphenylalanyl-L-leucine methyl ester 22.68g as an oil.

e) L-β,β-Diphenylalanyl-L-leucine methyl ester (Example 1d, 22.5g) was heated in a solution of 5.5M-hydrochloric acid (200ml) at 140°C for 24h under an atmosphere of nitrogen. The suspension was cooled to room temperature and the solid removed by filtration and dried to give L-β,β-diphenylalanine hydrochloride, 12.42g with an enantiomeric purity > 99.0% (as determined by hplc after derivatization by (+)-9-fluorenylethylchloroformate).

f) To a solution of 1M-lithium aluminium hydride in diethyl ether (40ml, 0.04mol) was added L-β,β-diphenylalanine hydrochloride (3.70g, 0.0133mol, Example 1e) over a period of 1h. The solution was heated at reflux for 1h, cooled to room temperature and to the solution was cautiously added

2M-sodium hydroxide (40ml). After filtering the solution through Celite, the residue was washed with ethyl acetate and the organic phase of the combined filtrates was washed with water, saturated brine and dried (MgSO_4). The solid which
5 formed on removal of the solvent *in vacuo* was washed with hexane to give (S)-2-amino-3,3-diphenylpropan-1-ol 2.52g. ^1H NMR (360MHz, CDCl_3) δ 7.36-7.14 (10H, m), 3.79 (1H, d, J = 10.5Hz), 3.6 (1H, m), 3.57 (1H, dd, J = 10.7Hz and 3.3Hz), 3.31 (1H, dd, J = 10.7Hz and 6.7Hz), m/z (CI^+) 228 ($\text{M}+\text{H}$).

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g) A solution of (S)-2-amino-3,3-diphenylpropan-1-ol (2.3g, 0.010mol, Example 1f) and di-*t*-butyldicarbonate (2.65g, 0.0122mol) in dichloromethane (25ml) was stirred at room temperature for 1h. The solid which formed on removal of the
15 solvent was recrystallized from diethyl ether to give (S)-2-*t*-butoxycarbonylamino-3,3-diphenylpropan-1-ol (2.85g). ^1H NMR (250MHz, CDCl_3) δ 7.34-7.15 (10H, m), 4.58 (1H, bd), 4.48 (1H, m), 4.1 (1H, d, J = 10.6Hz), 3.67 (1H, dd, J = 11.13Hz and 3.11Hz), 3.5 (1H, dd, J = 11.3Hz and 4.45Hz), 1.31 (9H, s).

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h) To a cooled solution (0°C) of (S)-2-*t*-butoxycarbonylamino-3,3-diphenylpropan-1-ol (2.04g, 6.2mmol, Example 1g) in tetrahydrofuran (50ml) and dimethylformamide (10ml) was added sodium hydride (0.187g, 80% suspension in oil)
25 over 15 minutes. After an additional 10 minutes 3,5-bis(trifluoromethyl)benzyl bromide (1.14ml) was added and the solution stirred at room temperature for 16h. The solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 and water. After washing the organic phase with
30 saturated brine and drying (MgSO_4), the solvent was removed *in vacuo* and the residue chromatographed on silica gel in ethyl

acetate/hexane (0:100 to 50:50) to give
(S)-2-t-butoxycarbonylamino-1-((3,5-bis(trifluoromethyl) phenyl)
methyloxy)-3,3-diphenylpropane, 2.92g.

5 i) A solution of (S)-2-t-butoxycarbonylamino-
1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-
diphenylpropane (2.92g, Example 1h) in trifluoroacetic acid
(20ml) was evaporated after 10 minutes. A solution of the
residue in CH_2Cl_2 was washed with 10% aqueous Na_2CO_3 ,
10 water, saturated brine and dried (MgSO_4). Removal of the
solvent *in vacuo* gave 2-amino-1-((3,5-bis(trifluoromethyl)
phenyl)methyloxy)-3,3-diphenylpropane.

15 j) To a solution of (S)-2-amino-1-((3,5- bis(trifluoromethyl)
phenyl)methyloxy)-3,3-diphenylpropane (8.6g, Example 1i) and
anhydrous K_2CO_3 (13.0g) in dimethylformamide (50ml) was
added methyl bromoacetate (4.5ml). The reaction was stirred at
room temperature for 0.75h then diluted with ethyl acetate
(200ml) and washed with water (4 x 100ml), brine (100ml), dried
20 over MgSO_4 and evaporated to dryness. The residual oil was
purified on silica gel eluting with petroleum ether-ethyl acetate
mixtures to give (S)-N-(1-((3,5-bis(trifluoromethyl)phenyl)
methyloxy)-3,3- diphenylprop-2-yl)glycine methyl ester as an oil
(7.61g). ^1H NMR (360MHz, CDCl_3) δ 7.77 (1H, s), 7.71 (2H, s),
25 7.42 (2H, d, $J = 7.4\text{Hz}$), 7.33-7.13 (8H, m), 4.44 (2H, s), 4.12 (1H,
d, $J = 7.2\text{Hz}$), 3.73-3.69 (1H, m), 3.63 (3H, s), 3.57-3.52 (1H, m),
3.53 (2H, d, $J = 6.7\text{Hz}$) and 3.44-3.36 (1H, m).

30 k) To a solution of the product of Example 1j (7.6g) in
anhydrous dimethylformamide (80ml) was added methyl iodide
(4.5ml) and anhydrous potassium carbonate (10.0g) and the

reaction stirred under N₂ at room temperature for 16 hrs. The reaction was diluted with ethyl acetate (200ml) and washed with water (4 x 100ml) and brine (100ml), dried over MgSO₄ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture to yield (S)-N-(1-((3,5-bis(trifluoromethyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine methyl ester. ¹H NMR (360MHz, CDCl₃) δ 7.76 (1H, s), 7.69 (2H, s), 7.37-7.11 (10H, m), 4.41-4.30 (2H, ABq, J = 12.6Hz), 4.20 (1H, d, J = 11.4Hz), 3.78-3.64 (2H, m), 3.56-3.36 (6H, m) and 2.48 (3H, brs).

1) To a solution of the product of Example 1k (1.5g) in tetrahydrofuran (30ml) was added potassium hydroxide (312mg) in water (10ml) and heated to reflux for 16 hrs. After evaporation of the solvent the residue was acidified by addition of hydrogen chloride (2N, 30ml) and the product extracted into diethyl ether (3 x 30ml), dried over magnesium sulphate and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with petroleum ether-ethyl acetate and methanol mixtures to yield (S)-N-(1-((3,5-bis(trifluoromethyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine. mp 61-63°C, m/z (CI⁺) = 526 (M+H) (CI⁻) = 524 (M-H). ¹H NMR (360MHz, DMSO) δ 7.99 (1H, s), 7.93 (2H, s), 7.49-7.10 (10H, m), 4.53-4.45 (2H, ABq, J = 13Hz), 4.20 (1H, d, J = 11.7Hz), 4.05-4.03 (1H, m), 3.53-3.42 (4H, m) and 2.32 (3H, s).

EXAMPLE 2

(S)-N-(1-(((3-t-Butyl-5-chloro)phenyl)methoxy)-3,3
diphenylprop-2-yl)-N-methylglycine acetate salt

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a) 4-t-Butyl-2-chloroaniline (30g) was dissolved in dichloromethane (1.2l) and the solution was cooled to -5°C. N-Chlorosuccinimide (21.7g) was added portionwise to the vigorously stirred solution and stirring was continued for 1h.
10 Dimethyl sulfide (36ml) was added to the solution (-5°C) and stirring was continued for a further 1h. The solution was then cooled to -65°C and triethylamine (27ml) was added. This solution was evaporated to half volume, washed successively with sodium hydroxide (1N), water and brine. The organic
15 solution was dried (MgSO₄) and evaporated *in vacuo* and the residue was purified on silica using hexane to 3% ether in hexane as eluent. This afforded 4-t-butyl-2-chloro-6-(methylthiomethyl)aniline (31.2g) as a red oil. ¹H NMR (250MHz, CDCl₃) δ 1.27 (9H, s, (CH₃)₃), 1.99 (3H, s, SCH₃), 3.69 (2H, s, CH₂SCH₃), 4.38 (2H, brs, NH₂), 6.92 (1H, d, J = 2.0Hz, Ar-H), 7.21 (1H, d, J = 2.0Hz, ArH). m/z (CI⁺) = 244 (M⁺+1, 100%).

25 b) 4-t-Butyl-2-chloro-6-(methylthiomethyl)aniline (1.3g) was dissolved in methanol (50ml) and Raney-nickel (prewashed to pH 7) was added portionwise until t.l.c. indicated all starting material had reacted (ether-hexane, 1:10). The Raney-nickel was removed by filtration through Celite and the filtrate was evaporated. The residue was dissolved in ether and washed with
30 brine, dried (MgSO₄) and evaporated. The residue was purified on silica using hexane and 5% ether in hexane as eluent to afford

4-t-butyl-2-chloro-6-methylaniline as a yellow liquid. ^1H NMR (360MHz, CDCl_3) δ 1.26 (9H, s, $(\text{CH}_3)_3$), 2.19 (3H, s, CH_3), 3.97 (2H, s, NH_2), 6.97 (1H, d, $J = 2.0\text{Hz}$, ArH), 7.14 (1H, d, $J = 2.0\text{Hz}$, ArH).

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c) 4-t-Butyl-2-chloro-6-methylaniline (1.97g) was dissolved in ethanol (50ml), sulphuric acid (1.88ml, conc.) was added dropwise and the resulting blue solution was heated at reflux. Sodium nitrite (1.72g) was added portionwise over 30 min. The resulting mixture was heated at reflux for a further 30 min, then cooled and was poured onto ice water and extracted with ether (2 x 50ml). The ethereal extract was dried (MgSO_4) and evaporated and the residue was purified on silica using hexane as eluent to afford 3-t-butyl-5-chlorotoluene as a colourless oil. ^1H NMR (360MHz, CDCl_3) δ 1.29 (9H, s, $(\text{CH}_3)_3$), 2.31 (3H, s, CH_3), 6.98 (1H, brs, ArH), 7.05 (1H, brs, ArH), 7.15 (1H, brs, ArH). MS (CI-) m/z 181 ($\text{M}^+ - \text{H}$, 100%).

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d) 3-t-Butyl-5-chlorotoluene (5.7g) was dissolved in carbon tetrachloride (80ml) and N-bromosuccinimide (5.56g) was added followed by benzoyl peroxide (750mg). This mixture was heated at reflux for 6h. The mixture was cooled, filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica using hexane as eluent to afford 3-t-butyl-5-chlorobenzyl bromide as a colourless liquid. ^1H NMR (360MHz, CDCl_3) δ 1.31 (9H, s, $(\text{CH}_3)_3$), 4.42 (2H, s, CH_2), 7.20 (1H, t, $J = 1.5\text{Hz}$, ArH), 7.26 (1H, t, $J = 1.5\text{Hz}$, ArH), 7.28 (1H, t, $J = 1.5\text{Hz}$, ArH).

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e) To a solution of (S)-2-t-butoxycarbonylamino-3,3-diphenylpropan-1-ol (Example 1g, 0.964g) and 3-t-butyl, 5-

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chlorobenzyl bromide (Example 2d. 0.701g) in dimethylformamide (2ml) was added sodium hydride (60% suspension in oil, 0.161g). After 16h at room temperature saturated NH_4Cl and ethyl acetate (50ml) were added and the organic phase was washed with saturated brine and dried (MgSO_4). After evaporation *in vacuo* the residue was purified on silica gel (eluting with 0-2% ethyl acetate in petroleum ether) to give (S)-2-butoxycarbonylamino-1-(((3-t-butyl-5-chloro)phenyl)methyloxy)-3,3-diphenylpropane. ^1H NMR (360MHz, CDCl_3) δ 7.3-7.1 (13H, m), 4.77 (1H, d, $J = 9.66\text{Hz}$), 4.6 (1H, bt), 4.40 (1H, d, $J_{\text{gem}} = 12.0\text{Hz}$), 4.31 (1H, d, $J = 12.03\text{Hz}$), 4.25 (1H, d, $J = 10.8\text{Hz}$), 3.4 (1H, dd, $J = 9.3, 2.9\text{Hz}$), 3.3 (1H, dd, $J = 9.3, 2.9\text{Hz}$), 1.31 (9H, s).

f) To a cooled (0°C) solution of the product of Example 2e (0.588g) in tetrahydrofuran (5ml) and dimethylformamide (1ml) was added sodium hydride (80% suspension in oil, 0.042g). After stirring the solution at 0°C for 0.5h methyl iodide (0.36ml) was added and stirred at room temperature for a further 16h. Water (50ml) and ethyl acetate (50ml) were added and the organic phase washed further with water, saturated brine and dried (MgSO_4). After evaporation *in vacuo* the residue was chromatographed on silica gel (eluting with 15% ethyl acetate in petroleum ether bp $60-80^\circ\text{C}$) to give (S)-2-(N-t-butoxycarbonyl-N-methyl)-1-(((3-t-butyl-5-chloro)phenyl)methyloxy)-3,3-diphenylpropane m/z 522, 524 ($\text{M}+1$).

g) The product of Example 2f (0.611g) was dissolved in 4M HCl in methanol (10ml). After 1h the solution was evaporated to dryness and the residue crystallised from ethyl acetate to give (S)-1-(((3-t-butyl-5-chloro)phenyl)methyloxy)-3,3-diphenyl-2-

methylaminopropane hydrochloride salt, mp 201-203°C. ^1H NMR (360MHz, DMSO- d_6) δ 7.57 (2H, d, $J = 7.38\text{Hz}$), 7.39-7.17 (11H, m), 4.5 (1H, bm), 4.46 (1H, d, $J = 12.3\text{Hz}$), 4.3 (1H, d, $J = 11.6\text{Hz}$), 4.32 (1H, d, $J = 12.2\text{Hz}$), 3.67 (1H, dd), 3.35 (1H, dd, $J = 11.07, 4.31\text{Hz}$), 2.46 (3H, s), 1.26 (9H, s).

h) To a solution of the product of Example 2g (0.46g) in dimethylformamide (5ml) was added anhydrous K_2CO_3 (0.31g) and methyl bromoacetate (0.050ml). After stirring the solution for 4h at room temperature, water (50ml) and ethyl acetate (50ml) were added and the organic phase washed with saturated brine and dried (MgSO_4). After evaporation *in vacuo* the residue was chromatographed on silica gel (eluting with ethyl acetate:hexane (1:5) to give (S)-N-(1-(((3-t-butyl-5-chloro)phenyl)methyloxy)-3,3-diphenylprop-2-yl)-N-methylglycine methyl ester m/z (CI^+) = 494, 496 ($\text{M}+\text{H}$). ^1H NMR (360MHz, CDCl_3) δ 7.38-7.04 (13H, m), 4.26 (1H, d, $J = 12.2\text{Hz}$), 4.20 (1H, d, $J = 10.8\text{Hz}$), 4.15 (1H, d, $J = 12.0\text{Hz}$), 3.7 (1H, m), 3.60 (1H, dd, $J = 9.93, 2.11\text{Hz}$), 3.51 (3H, s), 3.49 (1H, d, $J = 16.7\text{Hz}$), 3.35 (1H, d, $J = 16.7\text{Hz}$), 3.34 (1H, dd, $J = 9.90, 5.57\text{Hz}$).

i) To a solution of the product of Example 2h (0.12g) in methanol (10ml) was added 4M-NaOH (5ml). The solution was stirred at room temperature for 1h then methanol (10ml) added and the solution heated to boiling (for 2 minutes). To the cooled solution was added acetic acid (1ml), ethyl acetate (20ml) and saturated brine (20ml). The organic phase was dried (MgSO_4) evaporated *in vacuo* and the residue chromatographed on silica gel (eluting with a gradient of chloroform to chloroform:methanol:acetic acid (85:10:5). The fractions containing the product were evaporated to a small volume then

freeze dried from glacial acetic acid to give (S)-N-(1-(((3-t-butyl-5-chloro)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine acetate salt m/z (CI⁺) 480, 482 (M+H). ¹H NMR (360MHz, DMSO-d₆) 7.48 (2H, d, J = 7.16Hz), 7.41 (2H, d, J = 7.15Hz), 7.3-7.1 (9H, m), 4.34 (1H, d, J = 12.4Hz), 4.25 (1H, d, J = 12.3Hz), 4.17 (1H, d, J = 11.7Hz), 4.01 (1H, m), 3.4 (2H, m), 3.33 (2H, s), 2.30 (3H, s), 1.90 (3H, s), 1.26 (9H, s).

The following examples were prepared by a method analogous to that described in Example 2 using the appropriate benzyl bromide.

EXAMPLE 3

(S)-N-(1-((3,5-Dimethylphenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine

mp = 124-27°C, m/z (CI⁺) = 418 (M+H) ¹H NMR (360MHz, DMSO-d₆) δ 7.48 (2H, d, J = 7.2Hz), 7.41 (2H, d, J = 7.2Hz), 7.26-7.09 (6H, m), 6.67 (1H, s), 6.80 (2H, s), 4.27 (1H, d, J = 12.7Hz), 4.18-4.15 (2H, ABq, J = 6.3Hz), 4.03-3.85 (1H, m), 3.44-3.26 (4H, m), 2.29 (3H, s) and 2.22 (6H, s).

EXAMPLE 4

(S)-N-(1-(((3-chloro-5-methyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine

m.p. = 52-54°C, ¹H NMR (360MHz, DMSO-D₆) δ 7.48 (2H, d, 7.41 (2H, d, J = 7.3Hz), 7.23 (4H, ddd, J = 2.4, 7.3, (4H, m), 6.98 (1H, s), 4.31 (1H, d, J = 12.4Hz), 4.20 7.8, 12.4Hz), 4.00 (1H,

m), 3.44-3.28 (4H, m), 2.30 (3H, s). m/z (CI^+) = 438 (^{35}Cl , $M+H$), 440 (^{37}Cl , $M+H$).

EXAMPLE 5

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(S)-N-(1-(((3-bromo-5-methyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine

m.p. = 87-90°C, 1H NMR (360MHz, DMSO- D_6 , 353°K) δ 7.42
10 (2H, d, J = 7.3Hz), 7.32 (2H, d, J = 7.3Hz), 7.25 (1H, s), 7.19 (5H, ddd, J = 1.6, 7.3, 8.7Hz), 7.10 (2H, app.t, J = 7.3Hz), 6.95 (1H, s), 4.25 (2H, br s), 4.16 (1H, d, J = 11.0Hz), 3.89 (1H, m), 3.37 (2H, br d, J = 4.4Hz), 3.13 (2H, br, m), 2.24 (6H, s). m/z (CI^+) 482 (^{79}Br , $M+H$), 484 (^{81}Br , $M+H$).

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EXAMPLE 6

(S)-N-(1-((3,5-dichlorophenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine hydrochloride salt

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1H NMR (360MHz, DMSO- D_6) δ 7.65 (3H, d, J = 7.4Hz), 7.51-7.17 (10H, m), 4.86-4.82 (1H, m), 4.61 (1H, d, J = 11.7Hz), 4.42-4.28 (2H, ABq, J = 12.6Hz), 4.20-4.14 (1H, m), 3.88 (1H, d, J = 17.1Hz), 3.70-3.61 (2H, m) and 2.81 (3H, s). m/z (CI^+) = 458
25 ($M+H$), mp = 156-159°C.

EXAMPLE 7(S)-N-(1-(((3-methyl-5-vinyl)phenyl)methyloxy)-3,3-diphenylprop-2-yl)-N-methylglycine

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a) A solution of (S)-N-(1-(((3-bromo-5-methyl)phenyl)methyloxy)-3,3-diphenylprop-2-yl)-N-methylglycine (Example 5, 0.8g, 1.7mmol) and vinyl tributyl tin (0.54ml, 1.83mmol) in dry toluene (6ml) was degassed (N₂) for 10 min, then tetrakis(triphenylphosphine)palladium (0) (0.04g, 0.003mmol) was added and the mixture heated at reflux under N₂. After 3 h a further 0.04 g of tetrakis(triphenylphosphine) palladium (0) was added and reflux continued for 16h. The reaction mixture was cooled to room temperature, the solvent was evaporated *in vacuo* and the residue purified by chromatography on silica gel (hexanes-ethyl acetate 97:3 then 9:1 then 4:1) to provide (S)-N-(1-(((3-methyl-5-vinyl)phenyl)methyloxy)-3,3-diphenylprop-2-yl)-N-methylglycine methyl ester as an oil. ¹H NMR (250MHz, CDCl₃) δ 7.40-7.10 (10H, m), 6.94 (1H, s), 6.70 (1H, dd, J = 11.2, 17.6Hz), 5.74 (1H, d, J = 17.6Hz), 5.24 (1H, d, J = 11.2Hz), 4.36-4.10 (3H, m), 3.76-3.30 (8H, m), 2.46 (3H, br s), 2.34 (3H, s), m/z (CI⁺) 444 (M+H, 100%).

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b) (S)-N-(1-(((3-methyl-5-vinyl)phenyl)methyloxy)-3,3-diphenylprop-2-yl)-N-methylglycine methyl ester (Example 7a) was treated with potassium hydroxide as described in Example 1 to provide (S)-N-(1-(((3-methyl-5-vinyl)phenyl)methyloxy)-3,3-diphenylprop-2-yl)-N-methylglycine as a foamy solid, ¹H NMR (250MHz, CDCl₃) δ 7.37-7.14 (10H, m), 7.13 (1H, s), 7.07 (1H, s), 6.92 (1H, s), 6.66 (1H, dd, J = 11.0, 17.0Hz), 5.72 (1H, d, J =

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17.0Hz), 5.22 (1H, d, J = 11.0Hz), 4.36 (2H, dd, J = 11.8Hz), 4.26 (2H, dd, J = 11.8Hz), 3.99 (1H, d, J = 11.8Hz), 3.72 (1H, m), 3.50-3.16 (8H, m), 2.31 (3H, s), 2.29 (3H, s). m/z (CI⁺) 430 (M+H).

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EXAMPLE 8

(S)-N-(1-(((3-ethyl-5-methyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine

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(S)-N-(1-(((3-methyl-5-vinyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine (Example 7) was dissolved in methanol and hydrogenated for 2h at 40 psi using palladium on activated charcoal (10%) as catalyst. The reaction mixture was filtered through celite and the filtrate concentrated *in vacuo* to provide the title compound as an oily solid. ¹H NMR (250MHz, CDCl₃) δ 7.38-7.14 (10H, m), 6.94 (1H, s), 6.87 (2H, s), 4.33 (2H, m), 3.99 (1H, d, J = 11.2Hz), 3.71 (1H, br m), 3.48-3.14 (4H, m), 2.54 (2H, q, J = 7.3Hz), 2.31 (6H, brs), 1.21 (3H, t, J = 7.3Hz). m/z (CI⁺) 432 (M+H).

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EXAMPLE 9

(S)-N-(1-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)alanine

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The product of Example li was alkylated with methyl DL-2-bromopropionate as described in Example 1j and then saponified as described in Example 11 to give two separated diastereomers as freeze dried solids.

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Diastereomer A Found C, 57.17; H, 5.00; N, 2.14:

O₂₇H₂₅F₆NO₃ · 2.25(H₂O) requires C, 57.29; H, 5.25; N 2.47%.

¹H NMR (360MHz, DMSO-d₆) δ 8.03 (1H, s), 8.01 (2H, s), 7.55 (2H, d, J = 7.74Hz), 7.38-7.15 (8H, m), 4.63 (1H, d, J_{gem} = 12.9Hz), 4.51 (2H, m+d, J = 12.9Hz), 4.40 (1H, d, J = 11Hz), 3.79 (1H, q), 3.70 (1H, d), 3.5 (1H, dd), 1.38 (3H, d, J = 7.11Hz). m/z (CI⁺) = 526 (M+H), (CI⁻) = 524 (M-H).

Diastereomer B ¹H NMR (360MHz, DMSO-d₆) δ 8.0 (1H, s), 7.9 (2H, s), 7.41-7.10 (10H, m), 4.60 (1H, d, J_{gem} = 13.1Hz), 4.03 (1H, d, J = 11Hz), 3.16 (1H, dd), 1.00 (3H, d, J = 6.8Hz). m/z (CI⁺) = 526 (M+H), (CI⁻) = 524 (M-H).

EXAMPLE 10

(S)-2-(N,N-bis(carboxymethyl)amino)-1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenylpropane

The amine (Example 1i, liberated from the salt by partitioning between ethyl acetate and Na₂CO₃ solution followed by drying MgSO₄ and evaporation, 1.6g), K₂CO₃ (1.07g) methyl bromoacetate (0.7ml) in dimethylformamide (10ml) were heated to 100°C for 2h. The solution was diluted with ethyl acetate (100ml) and washed with water, saturated brine and dried (MgSO₄). After evaporation *in vacuo* the residue was purified by silica gel chromatography to give (S)-2-(bis((carboxymethoxy)methyl)amino)-1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenylpropane as an oil. ¹H NMR (360MHz, CDCl₃) δ 7.78 (1H, s), 7.69 (2H, s), 7.4-7.1 (10H, m), 4.41 (1H, d, J = 12.5Hz), 4.30 (1H, d, J = 11.5Hz), 4.20 (1H, d, J = 12.5Hz), 3.86 (1H, m), 3.7 (1H, d, J =

17.5Hz), 3.5 (1H, d, J = 17.5Hz), 3.5 (6H, s), 3.4 (1H, m). A solution of this oil (0.5g) in tetrahydrofuran (20ml) was treated with KOH (0.234g) in water (5ml) and the solution heated to reflux for 16h. The solution was concentrated *in vacuo* and on acidification to pH 2 with 6N-HCl gave the title compound as a solid. ¹H NMR (DMSO-d₆) δ 7.99 (1H, s), 7.94 (2H, s), 7.51 (2H, d, J = 7.38), 7.44 (2H, d, J = 7.31), 7.26-7.11 (6H, m), 4.55 (1H, d, J_{gem} = 12.9Hz), 4.38 (1H, d, J_{gem} = 12.9Hz), 4.28 (1H, d, J = 11.6Hz), 4.07 (1H, m), 3.46 (4H, dd, J_{gem} = 18.1Hz). m/z (FAB⁺) 570 (M+H), (FAB⁻) 568 (M-H).

EXAMPLE 11

(S)-N-(1-(((3-methoxy-5-methyl)phenyl)methyloxy)-3,3-diphenylprop-2-yl)-N-methylglycine

a) A refluxing solution of 3,5-dimethylanisole (13g), azoisobutyronitrile (1.6g) and N-bromosuccinimide (17g) in carbon tetrachloride (100ml) was irradiated with light for 6h. The solution was filtered and the solvent removed *in vacuo*. The residue was purified by chromatography on silica gel (eluting with 0-5% ethyl acetate - petroleum ether bp=60-80°C) to yield 3-bromomethyl-5-methylanisole.

b) The product of Example 11a was used to prepare the title compound by a method analogous to that described in Example 2. ¹H NMR (250MHz, CDCl₃) δ 7.42-7.20 (10H,m), 6.66(1H,s), 6.62(2H,s), 4.35(1H,d, J_{gem}=11.6Hz), 4.24 (1H,d, J_{gem}=11.7Hz), 4.42-4.08(2H,m), 3.79(3H,s), 3.64(1H,dd), 3.55(2H,s), 3.41(1H,dd,J=11.1, 6.5Hz) 2.5(3H,s), 2.32(3H,s). ¹H NMR (25MHz, DMSO d₆) δ 7.49 (2H,d J=7.11Hz), 7.42(2H,d J=7.12Hz),

7.26(6H,m), 6.63(2H,s), 6.60(1H,s), 4.31(1H,d,J_{gem}=12.1Hz),
4.19(1H,d,J=11.8Hz), 4.16(1H, d, J_{gem} =12.1Hz), 4.04(1H,m),
3.71(3H,s), 3.44-3.30(4H,m), 2.30(3H,s), 2.24(3H,s). m/z (CI⁺)=
434(M+H)

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EXAMPLE 12

(S)-N-(1-((3,5-bis(trifluoromethyl)phenyl)methoxy)-3,3-
diphenylprop-2-yl)-N-ethylglycine

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Ethyl iodide was used instead of methyl iodide to prepare
the title compound by a method analogous to that described in
Example 2. ¹H NMR (250MHz, DMSO d₆) δ 8.02(1H, s),
7.94(2H, s), 7.53 (2H, d, J=7.1Hz), 7.46 (2H, d, J=7.1Hz), 7.31-
7.10(6H, m), 4.56-4.45(2H, ABq, J=12.8Hz), J=7.0Hz).
4.42-4.36 (2H, m), 3.70-3.51(4H, m), 0.84(3H, t, J = 7.0 Hz).

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EXAMPLE 13

(R)-N-(1-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-3,3-
diphenylprop-2-yl)-N-methylglycine

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The title compound was prepared as described in Example 1
using D-β,β-diphenylalanyl-L-leucine methyl ester (Example 1d)
which after hydrolysis in a similar manner to that described in
Example 1e gave D-β,β-diphenylalanine hydrochloride. Using
the procedures described in Examples 1f-l D-β,β-diphenylalanine
hydrochloride was converted to the title compound m/z
(CI⁺)=526 (M+H). ¹H NMR identical to the product of Example
1. Chiral hplc (Chiral AGP, 10% MeCN in 10mM K₂HPO₄
pH6.5) >99% enantiomeric excess.

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EXAMPLE 14N-(3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1,1-diphenylbut-2-yl)-N-methylglycine

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a) To a cooled (-30°C) solution of N-t-butoxycarbonyl-β,β-diphenylalanine (13.8g) and triethylamine (28ml) in dimethylformamide (200ml) was added isobutylchloroformate (3.12ml) such that the temperature remained below -20°C. After 10 15min a solution of N,O-dimethylhydroxylamine hydrochloride (13g) in CH₂Cl₂ was added. The solution was stirred at room temperature for 18h whereupon it was diluted with ethyl acetate and washed successively with 10% aqueous citric acid, water, saturated NaHCO₃, saturated brine, and dried (MgSO₄). 15 Removal of the solvent *in vacuo* gave N-t-butoxycarbonyl-β,β-diphenylalaninyl-(N-methoxy,N-methyl)amide which was used without further purification. To a cooled (-10°C) solution of N-t-butoxycarbonyl-β,β-diphenylalaninyl-(N-methoxy,N-methyl)amide (5g) in tetrahydrofuran (130ml) was added 1M- 20 methylmagnesium chloride (13ml). The solution was stirred for 2h whereupon it was diluted with diethyl ether and a saturated solution of ammonium chloride was added. The organic phase was washed with water, saturated brine and dried (MgSO₄). The residue was chromatographed on silica (eluting with ethyl 25 acetate / petroleum ether b.p. 60-80°C 10%,20%,30%) to give 2-N-t-butoxycarbonylamino-1,1-diphenylbutan-3-one, ¹H NMR (CDCl₃,250MHz) δ 7.46-7.12 (10H,m,Ph), 4.94(1H,dd,J=8.7, 11.6Hz), 4.26(1H,d,J=11.7Hz), 1.91(3H,s), 1.27(9H,s).

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b) To a solution of 2-N-t-butoxycarbonylamino-1,1-diphenylbutan-3-one (2.74g, Example 14a) in methanol (100ml)

was added sodium borohydride (0.73g). After 4h the solution was diluted with ethyl acetate and washed with dilute HCl, water, saturated brine, and dried (MgSO₄). Removal of the solvent *in vacuo* gave 2-N-t-butoxycarbonylamino-1,1-diphenyl-3-hydroxybutane as a mixture of diastereoisomers (3 : 1). To a solution of the mixture of diastereoisomers (2.15g) and 3,5-bis(trifluoromethyl)benzyl bromide (1.8ml) in dimethylformamide (20ml) was added sodium hydride (0.304g, 60% suspension in oil). After 18h the reaction was quenched by addition of saturated ammonium chloride and the product extracted into ethyl acetate. The organic phase was washed with water (twice), saturated brine, and dried (MgSO₄). After removal of the solvent *in vacuo* the residue was purified by chromatography on silica (eluting with ethyl acetate / petroleum ether b.p. 60-80°C, 2%,5%) to give 2-N-t-butoxycarbonylamino-1,1-diphenyl-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)butane as a mixture of diastereoisomers (2 : 1).

c) A solution of 2-N-t-butoxycarbonylamino-1,1-diphenyl-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)butane (Example 14b, 1g) in dimethylformamide (5ml) was alkylated and deprotected in an analogous manner to that described in Example 2f,2g,2h,2i to give N-(3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-1,1-diphenylbut-2-yl)-N-methylglycine as a mixture of diastereoisomers which were separated by chromatography on silica (eluting with methanol in CH₂Cl₂ 0%,5%).

Diastereoisomer A: ¹H NMR (CDCl₃ 250MHz) δ
1.36(3H,d,J=5.7Hz), 2.51(3H,s), 3.32-3.45(2h,ABq, J=18Hz),
3.63(1H,dd,J=11Hz), 3.68(1H,dq),3.86(1H,d,J=12Hz), 4.38(1H,d,

J=11Hz), 4.51(1H,d,J=12Hz), 7.16-7.43(10H,m),7.71(2H,s),
7.84(1H,s).CHN analysis found C,62.36; H,5.05; N,2.61.
C₂₈H₂₇NO₃F₆ requires C,62.34; H, 5.05; N, 2.60%.

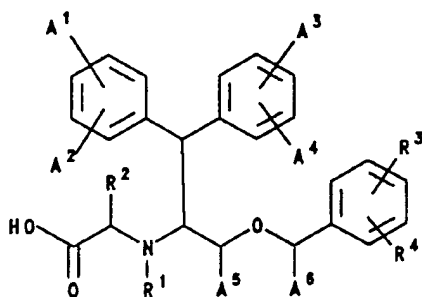
- 5 Diastereoisomer B: ¹H NMR (CDCl₃ 250MHz) δ
1.10(3H,d,J=6.9Hz), 2.44(3H,s), 3.26(1H,d, J=16Hz), 2.52(1H, d,
J=16Hz), 3.68(1H,dq),3.92(1H,dd,J=12.5Hz), 4.20(1H,d,
J=12.5Hz), 4.52-4.65(2H,ABq, J=12.5Hz), 7.10-
7.44(10H,m),7.74(2H,s), 7.82(1H,s).CHN analysis found C,61.85;
10 H,4.98; N,2.56. C₂₈H₂₇NO₃F₆ . 0.25(H₂O)requires C,61.82; H,
5.10; N, 2.57%.

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Claims

1. A compound of formula (I) as a salt or prodrug thereof:

5



(I)

wherein

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R^1 represents H, C_{1-4} alkyl or CH_2COOH ;

R^2 represents H or C_{1-4} alkyl, with the proviso that R^1 and R^2 are not both H;

20

R^3 and R^4 each independently represent H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, halo or trifluoromethyl;

A^1 , A^2 , A^3 and A^4 each independently represent H, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkoxy, halo or trifluoromethyl;

25

and A^5 and A^6 each independently represent H or C_{1-4} alkyl.

2. A compound according to claim 1 wherein A^1 , A^2 , A^3 , A^4 , A^5 and A^6 are each hydrogen.

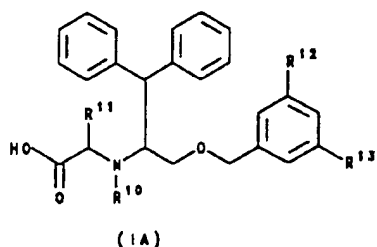
3. A compound according to claim 2 where R^2 is hydrogen or methyl.

30

4. A compound according to claims 2 or 3 wherein R^3 and R^4 are located at the 3- and 5- positions of the phenyl ring.

5. A compound of the formula (IA) or a pharmaceutically acceptable salt thereof:

- 38 -



wherein

R^{10} represents H, methyl or CH_2COOH ;

10 R^{11} represents H, methyl or ethyl, with the proviso that when R^{10} is H, R^{11} is not H; and

R^{12} and R^{13} each independently represent C_{1-6} alkyl, such as t-butyl, methyl or ethyl, C_{2-6} alkenyl, such as vinyl, C_{1-6} alkoxy, such as methoxy, halo, such as
15 chloro or bromo, or trifluoromethyl.

6. A compound selected from:

(S)-N-(1-((3,5-bis(trifluoromethyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

(S)-N-(1-((3-t-butyl-5-chloro)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

20 (S)-N-(1-((3,5-dimethyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

(S)-N-(1-((3-chloro-5-methyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

25 (S)-N-(1-((3-bromo-5-methyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

(S)-N-(1-((3,5-dichlorophenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

(S)-N-(1-((3-methyl-5-vinyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

30 (S)-N-(1-((3-ethyl-5-methyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

(S)-N-(1-((3,5-bis(trifluoromethyl)phenyl)methoxy)-3,3-diphenylprop-2-yl)alanine;

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(S)-2-(N,N-bis(carboxymethyl)amino)-1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenylpropane;

(S)-N-(1-((3-methoxy-5-methyl)phenyl)methyloxy)-3,3-diphenylprop-2-yl)-N-methylglycine;

(S)-N-(1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenylprop-2-yl)-N-ethylglycine;

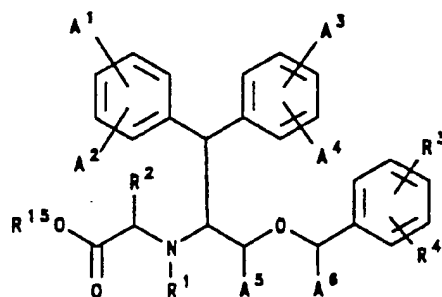
and pharmaceutically acceptable salts thereof.

7. A pharmaceutical compositions comprising one or more compounds of formula (I), or salts or prodrugs thereof, in association with a pharmaceutically acceptable carrier.

8. The use of a compound as claimed in any of claims 1 to 6 in the preparation of a medicament for the treatment of a disorder caused by an excess of tachykinin.

9. A method of treatment or preparation of physiological disorders associated with an excess of tachykinins which comprises a patient in need thereof of a tachykinin reducing amount of a compound according to any of claims 1 to 6.

10. A process for the preparation of a compound as claimed in any of claims 1 to 6 which comprises saponification of a compound of formula (II):



(II)

- 40 -

wherein R^1 , R^2 , R^3 , R^4 , A^1 , A^2 , A^3 , A^4 , A^5 and A^6 are as defined for formula (I) above and R^{15} represents C_1 - C_6 alkyl, using conventional methods.

INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/GB 93/02592

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C229/14 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 499 313 (MERCK SHARP & DOHME) 19 August 1992 see examples, especially 5,13,27,28,31-34,37-39,43-47, claims 1,12 ---	1,4,8
A	DE,A,20 35 535 (CENTRE EUROPEEN DE RECHERCHES MAUVERNAY) 28 January 1971 see page 18, last paragraph - page 19, line 8; claims 1,2; examples ---	1,8
A	EP,A,0 436 334 (PFIZER) 10 July 1991 cited in the application ---	
A	EP,A,0 394 989 (FUJISAWA PHARMACEUTICAL CO.) 31 October 1990 cited in the application ---	
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

- * "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- * "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- * "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- * "&" document member of the same patent family

Date of the actual completion of the international search

11 March 1994

Date of mailing of the international search report

25. 03. 94

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Authorized officer

Seufert, G

INTERNATIONAL SEARCH REPORT

Inter nal Application No

PCT/GB 93/02592

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,93 01160 (MERCK SHARP & DOHME) 21 January 1993 see claims 1,3,10,15; examples 44,35 -----	1-5,7-10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB93/02592

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 9 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 93/02592

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0499313	19-08-92	JP-A- 5078354 US-A- 5242930 CA-A- 2060949	30-03-93 07-09-93 12-08-92
DE-A-2035535	28-01-71	FR-A- 2054507	23-04-71
EP-A-0436334	10-07-91	WO-A- 9109844 EP-A- 0558156	11-07-91 01-09-93
EP-A-0394989	31-10-90	JP-A- 3027399 US-A- 5164372	05-02-91 17-11-92
WO-A-9301160	21-01-93	AU-A- 2244092 CA-A- 2110513 EP-A- 0522808 CA-A- 2110514 WO-A- 9301159 WO-A- 9301169 WO-A- 9301165	11-02-93 21-01-93 13-01-93 21-01-93 21-01-93 21-01-93 21-01-93